Management of drug-resistant tuberculosis

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Abstract The emergence and spread of drug-resistant strains of *Mycobacterium tuberculosis* (*M. tuberculosis*) have become tremendous challenges for clinical and programmatic tuberculosis (TB) management. Until recently, TB diagnosis was largely based on 120-year-old smear microscopy, and treatment was based on a limited number of drugs developed prior to 1970. During the past few years, we have witnessed a revolution in the ability of laboratories to detect TB and anti-TB drug resistance. Furthermore, after several years of silence, several new anti-TB drugs have recently appeared on the scene, offering hope for patients with very limited therapeutic options. There is also new evidence supporting the appropriate use of existing drugs in the treatment of MDR-TB and a better understanding of the relevance of additional resistance beyond extensive drug resistance patterns. In this article, we review the management of drug-resistant TB and highlight recent developments concerning its diagnosis and treatment.

Keywords Tuberculosis · Drug-resistant · MDR-TB · XDR-TB · Management · Diagnosis · Treatment · Review · Advances · Infection Control · Transmission · Cure

Introduction

Multidrug-resistant tuberculosis (MDR-TB), defined as tuberculosis (TB) that is resistant to at least rifampicin and

isoniazid, and extensively drug-resistant TB (XDR-TB), defined as MDR-TB that is also resistant to fluoroquinolone and any second-line injectable anti-TB drug, have become tremendous challenges for clinical and programmatic TB management as well as an enormous threat to global TB control.

The inadequate management of patients with susceptible TB, poor TB infection control measures, and the persistent high prevalence of HIV in some settings have allowed the number of M-XDR/TB cases to increase year after year.

According to World Health Organization (WHO) estimates, in 2011 MDR-TB accounted for 3.7 % of new TB cases and 20 % of re-treated cases [1]. Additionally, by the end of 2012, there were 84 countries reporting at least one case of XDR-TB [1], and isolates with increased patterns of drug resistance (resistance to 10 drugs) have become increasingly frequent in certain settings [2–5]. In 2011, 60,000 new MDR-TB cases were reported, and this represented less than one-fifth of estimated cases [1]. Furthermore, only about 20 % of the estimated MDR-TB cases were enrolled in treatment, and successful outcomes were reached in just 46 % of cases [1]. Most MDR-TB cases, in fact, occur in resource-constrained countries with very limited capacity to diagnose resistance and little access to second-line drugs (SLD). DR-TB cases need longer and more toxic treatment, and usually experience poorer outcomes.

This is especially evident in patients co-infected with HIV, in patients where diagnosis and access to treatment are delayed until the disease has advanced significantly, and in patients who are not properly managed [6]. It can be very difficult to standardize the management of these patients, who usually present with various patterns of resistance and a wide range of clinical conditions and comorbidities. Additionally, the situation is complicated by the low clinical reliability of drug susceptibility testing (DST) for many SLDs, delays in obtaining DST results, and the limited efficacy and frequent toxicity of many SLDs [7••].

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There still exists a large unmet need in the area of DR-TB management, and new needs continue to emerge as a consequence of the dynamic interactions among *M. tuberculosis*, the environment, anti-TB drugs, and humans (Table 1). Fortunately, there have been greater efforts in recent years to address these needs. After many stagnant years, TB is once again in the spotlight with the emerging global threat of MDR/XDR-TB as well as recent advances in diagnosis and, potentially, in treatment. Hopefully, this new evidence will be used to improve the clinical management of MDR/XDR-TB.

Diagnosis of drug-resistant tuberculosis

There are no differences between susceptible and resistant TB in terms of clinical presentation, smear microscopy results, and radiographic features. MDR-TB diagnosis should start with the identification of patients who are more likely to be infected with resistant strains of *M. tuberculosis*. Previously treated patients, especially treatment failures, and patients with MDR-TB case exposure are at highest risk of anti-TB drug resistance. Other groups at greater risk of harboring resistant strains include patients who remain smear-positive at the end of the second month of category I treatment, those who present comorbidities associated with malabsorption or HIV, and those whose treatment is irregular due to poor adherence or frequent drug stock-outs [7•, 8, 9].

The primary method of identifying resistant strains is through bacterial culture (performed in solid or liquid culture medium) and drug susceptibility testing (DST) based on phenotypic detection of bacterial growth in the presence of different anti-TB drugs. These techniques are costly and not always easily accessible, however, and they are at high risk of contamination and have very long turnaround times (at least 2–4 months and 2–3 weeks, respectively). Additionally, with the exception of rifampicin, isoniazid, fluoroquinolones, and aminoglycosides, the DST for the other anti-TB drugs is limited in reproducibility and clinical reliability, with a poor correlation between in vitro and in vivo results. Therefore, a detailed analysis of the history of anti-TB drugs taken by the patient in the past exploring possible monotherapies and the history of drug use in the country are valuable complements to the information provided by DST results [7•, 9, 10•, 11].

New rapid molecular methods have recently become available and have been widely implemented in some settings. Line probe assays (INNO-LiPA Rif.TB® and GenoType MTBDRplus®) and the GeneXpert MTB/RIF® system are molecular PCR-based tests that simultaneously diagnose TB

Table 1 Ongoing needs in MDR/XDR-TB management

1. Improving susceptible TB management to increase the likelihood of treatment success and reduce the risk of drug resistance selection and amplification.
2. Early diagnosis of TB and detection of drug resistance in order to ensure prompt initiation of proper treatment.
3. Better use of existing FL and SL drugs as well as new drugs that offer a cure for patients with extended patterns of resistance.
4. Reviewing standardized and individualized regimens – including failure with SLD treatment – in light of changing resistance landscapes.
5. Reducing side effects related to SLD use and improving SLD management.
6. Improving management of DRTB in patients co-infected with HIV – interactions, side effects, and adherence-related issues.
7. Identifying and validating new models of care for MDR/XDR-TB in order to expand access to DR-TB treatment and improve patient adherence and follow-up.
8. Enhancing additional support (nutritional, psychological, social, palliative care).
9. Better defining the role and timing of surgery in the management of DR-TB.
10. Identifying ways to strengthen TB infection control measures that may be accessible in limited-resource settings.
11. More evidence on MDR/XDR-TB management in special situations, such as in children, in the presence of co-morbidities such as diabetes, or during pregnancy, including evidence of the consequences of MDR-TB treatment during pregnancy.
12. More evidence on what prophylaxis has to be offered to contacts of MDR/XDR-TB cases.
13. Reviewing the definitions of drug-resistance TB and its outcomes.
14. Shorter effective and well-tolerated regimens for DR-TB in order to increase treatment completion and successful outcomes.

and detect resistance to INH and/or RIF. This is accomplished through the detection of *M. tuberculosis* DNA in the specimen and identification of specific gene mutations responsible for resistance to RIF in the case of GeneXpert, and resistance to RIF and INH in the case of GenoType. The main advantage of these systems is the short turnaround time (2 days with GenoType and 2 hours with GeneXpert). Line probe assays require properly configured molecular laboratories, while GeneXpert can be performed at a peripheral level without special laboratory facilities, and thus could have an enormous impact in TB and RIF resistance detection. As approximately 95–98 % of *M. tuberculosis* RIF-resistant strains also show resistance to INH, the identification of RIF resistance serves as a surrogate diagnosis of MDR-TB. In light of this, the World Health Organization has recently published revised case definitions [12].

As recently as 2010, very promising results were published in studies from four countries with a high prevalence of MDR-TB, in which GeneXpert MTB/RIF® was shown to have identified 98.2 % of smear-positive and 72.5 % of smear-negative TB cases, correctly detecting 97.6 % of cases with

rifampin-resistant strains [13]. These results were confirmed by a larger study involving more than 6,000 patients from 6 countries, where excellent sensitivity was also indicated for patients with HIV co-infection, and where the median time to treatment for smear-negative TB was reduced from 56 to 5 days [14•]. In 2011, WHO recommended Xpert MTB/RIF as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB [15]. Since then, several studies have shown that GeneXpert MTB/RIF® offers additional value in the diagnosis of extra-pulmonary TB and in detecting TB in children [16, 17]. A recent study [18] of more than 1,000 patients with extra-pulmonary TB found that GeneXpert had greater than 85 % sensitivity in tissue biopsies, urine samples, pus, and cerebrospinal fluids, although lower than 50 % sensitivity in cavitory fluids, as compared to culture.

A limiting factor in all molecular methods is that they cannot be used for monitoring treatment because, as a PCR, they do not distinguish between live and dead bacilli, and so they can be used only for diagnosis. However, GeneXpert can be used for detecting RIF resistance in patients who are not converting bacteriologically during treatment for susceptible TB, especially in the case of failure. Furthermore, in the case of GenoType MTBDRplus® information regarding possible resistance to INH can be very relevant at the end of the second month of category I treatment for patients who are still smear-positive. In fact, the early detection of mono-resistance to INH but no resistance to RIF can alert clinicians to avoid shifting to the standard continuation phase with just INH+RIF, thereby avoiding RIF monotherapy, drug resistance amplification, and MDR-TB development [7••].

In many settings during the past two years, the large-scale implementation of these rapid molecular tests – and GeneXpert in particular – has led to a two- to threefold increase in the detection of MDR-TB cases [19••]. With the facilitation of MDR-TB diagnosis that these tools enable, we must ensure that an adequate number of quality-assured SLDs are available to treat the growing patient population and that there are enough skilled health professionals to manage these cases.

Lastly, another potential contribution of the GenoType MTBDRsl is the detection of resistance to fluoroquinolones and second-line injectables [20, 21]. However, given the suboptimal sensitivity (despite very high specificity) and lack of capacity to identify resistance to specific individual second-line injectables, currently the MTBDRsl test should be used only as a triage test to guide further therapeutic decisions and not as a replacement for phenotypic DST.

Treatment of drug-resistant tuberculosis

All forms of TB should be treated with a combination of drugs to avoid the selection of naturally resistant mutant bacilli and the development of drug resistance, and treatment should be

of sufficient duration to kill all populations of bacilli, depending on the different metabolic conditions, and to avoid relapse. In the case of a drug-resistant TB regimen, the number of drugs and the total treatment duration depend on the bactericidal and sterilizing activities of the specific TB drug [22]. Drug selection should follow rational criteria, and it will depend on the availability of drugs likely to be effective in a given patient. Unfortunately, the choice of drugs narrows as the pattern of drug resistance becomes more extensive. Thus far, there have been no randomized clinical trials comparing different regimens and drugs. Therefore, most of the current evidence and recent recommendations are based on expert opinions and personal experiences, at times with limited consensus [23••].

Designing a regimen for MDR-TB – selection of drugs

From a bacteriologic point of view, 3 active second-line drugs may be sufficient to cure MDR-TB, but because some drugs may be compromised or very weak, it is important to include at least 4 drugs likely to be effective [23••]. In fact, more drugs may be needed in some cases – for instance, with many drugs that are weak or have doubtful efficacy. The current WHO guidelines recommend a standardized MDR-TB treatment regimen with at least 4 likely effective drugs, including a second-line-injectable in the intensive phase, a fluoroquinolone, a thioamide, and either cycloserine or PAS plus pyrazinamide [24, 25].

Anti-TB drugs are organized into 5 groups, primarily on the basis of efficacy, route of administration, availability, cost, and tolerability [7••, 23••, 26•, 27, 28••] (Table 2). In designing a MDR-TB treatment regimen, drugs likely to be effective (because they are new to the country, have not been taken previously by the patient, or because of DST results, taking into account the limited clinical reliability of DST for SLD, ETB, and PZA) should be included according to the hierarchy of drug groups.

Group 1: first-line anti-TB drugs

PZA should be included and ETB should be considered (Table 2). High-dose INH may be effective [29, 30•] in the case of low drug-resistance levels – as in the case of mutations in the *inhA* gene and not in the *KatG* gene (both identifiable by GenoType). Mutations in *InhA*, in fact, confer low levels of resistance to INH and frequently high levels of resistance to thionamides [31]. Rifapentine cannot be recommended, given its complete cross-resistance with rifampicin. On the contrary, strains resistant to rifampicin may be susceptible to rifabutin in some cases, but due to limited availability and lack of clinical evidence, this drug should not be routinely recommended [26•].

Table 2 Rational classification and use of anti-tuberculosis drugs (based on World Health Organization guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. World Health Organization Document 2008;WHO/HTM/TB/2008.402:1–247 and Caminero JA, Sotgiu G, Zumla A, Migliori GB. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. *Lancet Infect Dis* 2010;10:621-9)

Groups of anti-TB Drugs	How to use
Group 1 – First-line drugs/oral drugs: Isoniazid (H), Rifampicin (R), Ethambutol (E), Pyrazinamide (Z)	<ul style="list-style-type: none"> • Use Z and evaluate the use of E (depending on the medication history), but neither should be considered as one of the 4 main effective drugs. • E should be considered especially in patients who previously received only category I regimen.
Group 2 - Fluoroquinolones: Ofloxacin (Ofx), Levofloxacin (Lfx), Moxifloxacin (Mfx), Gatifloxacin (Gfx).	<ul style="list-style-type: none"> • Include just one drug of this group • Preferably high dose Lfx (1 gr), or Mox. • It must always be included in a regimen for MDR/XDR-TB. • It must be considered as one of the 4 main effective drugs in MDR-TB. • It must not be considered as one of the 4 main effective drugs in XDR-TB.
Group 3 – Second-line injectables: Aminoglycosides: Kanamycin (Km), Amikacin (Ak) Cyclic Polypeptides: Capreomycin (Cm)	<ul style="list-style-type: none"> • Include just one drug of this group. • It must always be included in a regimen for MDR/XDR-TB. • It must be considered as one of the 4 main effective drugs in MDR-TB. • It must not be considered as one of the 4 main effective drugs in XDR-TB, because of the high cross-resistance among them.
Group 4 - Other Second Line Drugs: Thionamides: Ethionamide(Eto) / Prothionamide (Pto), Cycloserines (Cs) / Terizidone (Trd), p-aminosalicylic acid (PAS)	<ul style="list-style-type: none"> • Add as many as needed to complete an effective 4 drug regimen. • Always prefer Eto/Pto, if considered effective, and then Cs/Tz, and finally PAS.
Group 5 - Reinforcement Drugs: Linezolid (Lzd), Clofazimine (Cfz), Imipenem or Meropenem/Cilastatin (Ipm or Mrp/Cln), Amoxicillin clavulanate (Am/Cl)	<ul style="list-style-type: none"> • Use only if unable to complete an effective 4-drug regimen using drugs from Groups 1, 2, 3, and 4. • If available, Lzd should be the first choice among Group 5 drugs, followed by Cfz. • High doses of INH should not be included in this group. • Bedaquiline could also be considered in this group.

Group 2: Fluoroquinolones (FQs)

Just one drug of this group should be included. Cross-resistance among FQs is probably incomplete, and about 50 % of strains resistant to ofloxacin are susceptible to high doses of levofloxacin (Lfx) and moxifloxacin (Mfx) [32]. Unfortunately, most laboratories test resistance to ofloxacin only, which does not provide information useful in therapeutic decision-making because ofloxacin is seldom used in the treatment of MDR-TB. Thus far, there have been no studies evaluating the cross-resistance between Lfx and Mfx. High doses of Lfx show extended early bactericidal activity similar to that of Mfx and higher still than that of INH [33]. Mfx, however, carries better sterilizing capacities [34, 35] and excellent concentration in the tissues (better than Lfx). Unfortunately, Mfx is generally more costly and less available in limited-resource settings.

FQs are essential components of the regimen, and their use has been associated with more favorable outcomes in both MDR and XDR-TB cases [36•, 37•]. The importance of late-generation FQs over second-line injectables (SLIs) in successful outcomes of MDR-TB treatment is well-documented in a recent publication of Falzon et al. [38•]. The authors evaluated approximately 7,000 MDR-TB patients from 26 centers and found that treatment success rate was higher in MDR-TB with no additional resistance (64 %), and

then decreased progressively to 56 % for MDR-TB resistant to SLIs only, to 48 % for MDR-TB resistant to FQs only, to 40 % for XDR-TB patients. Therefore, a late-generation FQ should always be included in a DR-TB regimen, and should be considered as one of the 4 main effective drugs in MDR-TB but not as one of the 4 main effective drugs in XDR-TB.

Group 3: Second-Line Injectables (SLIs)

Just one drug of this group should be included. They are all bactericidal, with high levels of toxicity. TB strains resistant to streptomycin (Str) almost always remain susceptible to the other SLIs. Strains resistant to capreomycin (Cm) frequently remain susceptible to kanamycin (Kn) and amikacin (Ak). Strains resistant to Ak are resistant to Cm and Kn. Strains resistant to Kn show different levels of resistance to the other SLIs. Based on these cross-resistance patterns, the selection of these drugs should logically start with Str, followed by Cm, then Kn, and finally Ak. Streptomycin is no longer recommended, given the high rate of resistance (50 % of strains resistant to INH also show worldwide resistance to Str) and the lack of reliable laboratory testing [7•, 26•]. Unfortunately, Cm is more costly and less available than the remaining two SLIs. Therefore, Kn is the most frequently used SLI, followed by Ak. A DR-TB regimen should always include a SLI, and this should be considered as one of the 4 main effective drugs in MDR-TB

but not as one of the 4 main effective drugs in XDR-TB due to the possibility of cross resistance.

Group 4

This group includes three classes of drugs: the thionamides (ethionamide, Eto; or prothionamide, Pto); cycloserine (Cs) or terizidone (Trd); and p-aminosalicylic acid (PAS). Thionamides should be selected first [24, 25] because they are more bactericidal, better tolerated, and less expensive than the other group 4 drugs. However, their efficacy is adversely affected by the presence of an *inhA* mutation [31], which can be detected by GenoType. The next selection should be cycloserines or terizidone, which are bacteriostatic with limited toxicity and no cross-resistance with other compounds. PAS should be the last choice due to its poor toxicity profile and limited effectiveness. The primary role of this drug is to protect the other components in the regimen from resistance amplification. We could speculate that PAS should probably be moved to a less relevant drug group.

Group 5

This is a very heterogeneous group and includes drugs with limited experience in TB and low efficacy or high toxicity profiles. Based on effectiveness, potential adverse reactions, and cost, it was previously thought that the sequence of introduction of this group of drugs should be: clofazimine (Cfz), amoxicillin-clavulanate (Amx/Clv), linezolid (Lzd), carbapenems (imipenem/meropenem), clarithromycin, and then thioacetazone [7•, 26•]. However, in light of emerging evidence of their ability to provide support in M-XDR/TB treatment and their increasing availability in limited-resource settings, group 5 drugs should probably be reconsidered. Based on their effectiveness, without considering cost and adverse reactions, the sequence of introduction should begin with linezolid, followed by clofazimine, then carbapenems, and eventually amoxicillin-clavulanate. Although published evidence is still limited to a small number of patients and cost is a high barrier in some settings, there have been increasingly excellent experiences with regimens including linezolid [39•, 40•, 41]. Adverse reactions (mainly hematological toxicity and polyneuritis) are sometimes a concern [42], but a reduced Lzd dose or initial dose adjustment appear to have no negative effect on outcomes and can improve tolerability [39•, 43–45]. We believe that linezolid deserves a higher ranking among anti-TB drugs and, that if price were not a limitation, it should be considered among groups 2 (FQs) and 3 (SLIs).

The potential role of clofazimine has recently been considered in short-duration MDR-TB treatment regimens [30•], and this was addressed in depth in the recent review by Gopal et al. [46•], but limited availability precludes wider use of the drug. Finally, although there is very little published

experience with meropenem clavulanate [47–50], the results of in vitro studies are encouraging and have shown very good sterilizing activity. This drug could be better explored if price and availability were of less concern.

Finally, it is worth mentioning the new anti-TB drug bedaquiline, active against both susceptible and resistant *M. tuberculosis* strains. The drug just recently became available, and thus far has been relegated to compassionate use for selected patients in certain countries. Expectations for bedaquiline have been so high that the World Health Organization has recently published recommendations on its use in patients with MDR-TB resistance and extended resistance beyond MDR-TB [51].

Individualized versus standardized regimens

MDR-TB treatment can be standardized in order to facilitate prescription and prompt initiation, especially in settings with numerous cases and few skilled physicians. Standard regimens should be established for new MDR-TB cases where there is no known contact with an MDR-TB source and in patients who have previously received only FLDs. However, individualized regimens are better suited to patients who have received MDR-TB treatment in the past (with various FLDs and/or SLDs) [7•, 23•]. Experiences in countries with widely implemented standardized MDR-TB regimens have been very positive [30•, 52, 53]. In settings where expanded patterns of resistance are becoming more frequent, it may also be necessary to standardize regimens for patients failing MDR-TB standardized treatment and for new XDR-TB cases in order to facilitate the best management of these cases with the limited options available.

Duration of treatment

According to current WHO MDR-TB guidelines, duration of treatment should include an intensive phase (IP) of at least 8 months and a total duration of at least 20 months [24, 25]. It should be noted that this recommendation is based on very low-quality evidence and that the supporting data was not able to provide information on whether a minimum-duration intensive phase, post-conversion, could influence outcomes [24]. There is increasing evidence based on expert opinion that shorter treatment duration is adequate, especially in the intensive phase. In fact, although injectable drugs are fundamental in DR-TB treatment, the need for injection and drug-related toxicity warrants great caution regarding length of use [54]. Although there have been no studies analyzing the effectiveness and toxicity of different durations for injectables, it seems certain that toxicity increases with dose accumulation [55]. The concentration of these drugs is much higher in the urine and the ear than in the blood, and generally permanent

auditory and vestibular damage, as well as reversible nephrotoxicity, are frequent occurrences [54].

From a bacteriologic point of view, 4 drugs should be given during the intensive phase (IP) to ensure that, during a period of high bacillary load, not only all susceptible bacilli are killed, but also naturally resistant mutants are eradicated. When the bacterial load has been reduced to a minimum, however, it is possible to continue with only 2–3 drugs (depending on their bactericidal and sterilizing activity). In fact, in the presence of low bacillary load, there is little to no likelihood of naturally resistant mutants. Therefore, if smear conversion occurs very early (first 2–4 months), it is likely because the organisms are susceptible to FQs and the other drugs, and it would be reasonable to shift to the continuation phase (CP) when smears become negative. Conversely, if conversion occurs later (after 5–6 months), it is likely due to the fact that FQ is ineffective, and the early suspension of the injectable would cause the regimen to become too weak. In these cases, it would be better to extend the injectable duration to 6–12 months after the conversion of the cultures [7•]. When standardizing recommendations, there is a tendency to recommend a fixed injectable duration (6–8 months) [7•]. Although this strategy is justified from a programmatic perspective, it results in many patients receiving excessive doses of a toxic and uncomfortable drug, while others may be receiving insufficient doses. Recent publications from high-HIV-prevalence settings showed 89 % culture conversion within the first 6 months, with no difference regarding HIV status (median time to conversion of 62 days) [56]. Data from 5 DOTS-Plus pilot projects showed that among 1,385 positive sputum-culture cases of MDR-TB, 83 % experienced at least one conversion during treatment, and the median time to conversion was 3 months [57]. Standardized duration of the intensive phase is likely necessary in the initial implementation of an MDR-TB program while countries are building experience and capacity in the management of M/XDR-TB cases. Recommendations may be slightly modified as experience is consolidated. The length of injectable should be linked to conversion of the smear (or possibly culture), and probably not fixed at 8 months.

Ak and Str have a very good post-antibiotic effect (the effect of Kn and Cpm is unclear) [58], and therefore they can be administered 3 times weekly instead of daily. To date, there is no published evidence that this approach can reduce the adverse reactions related to injectables. Peloquin et al. found no differences in drug-related toxicity when injectables were administered daily versus 3 times weekly [55]. There is increasing evidence, however, that intermittent injectables cause fewer adverse reactions, while at the same time producing comparable outcomes (M. Rodriguez, Dominican Republic NTP, personal communication).

Finally, we'd like to highlight the interesting findings in a very recent publication by Falzon et al. [38•], where treatment success in XDR-TB patients was shown to be

highest when duration of the intensive phase was 6.6–9.0 months and total treatment duration was 20.1–25.0 months, suggesting that treatment duration for XDR-TB and MDR-TB may be similar.

Surgery as support in DR-TB treatment

Surgery has a limited role in the management of drug-resistant TB. It is indicated only in the presence of three conditions: four likely effective drugs are not available, the lesion is localised and there is sufficient respiratory reserve. Although these three criteria are rarely present, they do occur in some XDR-TB cases. Even in this situation, however, it is important to consider that surgery implies high morbidity/mortality and that the lesions are not completely sterilized [7•, 23•].

Surgery is likely to have a greater impact in the case of XDR-TB where pharmacological options are extremely limited, and surgery may help to achieve a cure [59•, 60]. It is also important to remember that a successful outcome in a surgical approach will strongly depend on the skills of the surgical and anesthesia teams [61], and that quality surgery can seldom be performed in countries with limited resources.

The optimal time to perform surgery in DR-TB patients has not yet been determined, but in most circumstances, surgery is recommended at the time of lowest bacillary load, ideally after sputum conversion. Early surgical intervention in DR-TB is more likely to produce a cure, as it is possible to physically reduce the bacillary load and increase the chance that even a weak regimen may be effective. On the other hand, earlier surgical intervention may lead to more complications.

Management of drug-resistant tuberculosis in special situations/special care in DR-TB management

Some situations may be considered “special” because of slightly different clinical management needs. Situations such as TB/HIV co-infection, pregnancy, extra-pulmonary TB, TB in children, and MDR-TB contact may require different management strategies. These are summarized in Table 3.

Conclusions

Recent advances in the diagnosis and treatment of DR-TB have been important steps forward in the management of MDR-TB. However, it is essential that governments, stakeholders, donors, and the pharmaceutical industry are united in a firm commitment to closing the gap between the number of estimated cases and the number enrolled in treatment, and to provide all MDR and XDR-TB patients with timely access to effective treatment and potential cure. The

Table 3 MDR-TB management in special situations and special care in MDR-TB management

TB in contacts of DR-TB patients	<ul style="list-style-type: none"> • Contacts of patients with MDR-TB, and who develop active TB, are very likely to have MDR-TB as well (65–85 % of cases). • However, in some cases contacts may show a different pattern of resistance: they can have a completely susceptible TB, or even XDR-TB, depending on when the infection occurred, and with the possibility that infection occurred in the community with a different source. • In MDR-TB contacts who develop TB, culture and DST should be performed and, while awaiting the results, started on the same MDR-TB regimen as the index case. The regimen should then be adjusted later according to the DST results.
MDR-TB and HIV co-infection	<ul style="list-style-type: none"> • There are no problems with the interactions of rifampicin (potent Cyt.P450 inducer) and protease inhibitors/NNRTIs, given that MDR-TB is by definition resistant to RIF and does not need to include RIF in the regimen. • Overlapping toxicity and increased side effects can occur during M-XDR/TB-HIV co-treatment. For instance: potential hepato-toxicity (PIs, NNRTIs and thionamides), nephrotoxicity (tenofovir and SL Injectables), psychiatric disturbances (efavirenz and cycloserine), myelosuppression and mitochondrial toxicity (NRTIs such ddI, d4T and AZT and linezolid) and others. • Antiretroviral treatment-ART should be initiated in DR-TB/HIV patients irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of anti-TB treatment. • IRIS (immuno-reconstitution inflammatory syndrome) might appear more frequently, as soon as the ARV treatment is initiated in patients receiving anti-TB drugs.
DR-TB and diabetes	<ul style="list-style-type: none"> • Diabetes is a recognized risk factor for TB (2–5 times higher risk), for atypical presentation of TB disease and for worst outcomes of its treatment. • Screening for TB should be performed in diabetic patients in order to detect TB early and prompt initiation of treatment. TB patients should be screened for diabetes, also. • Close follow up of TB patients with diabetes should be provided, given the increased risk of side effects—especially renal failure and neuropathy.
MDR-TB and pregnancy	<ul style="list-style-type: none"> • Initial pregnancy testing for all women of child-bearing age with MDR-TB. • Given the limited knowledge about the potential teratogenesis and toxicity of SLD for the fetus, treatment ideally should be avoided during the first trimester. However, risks and benefits need to be evaluated: in the presence of life-threatening conditions such advanced disease, respiratory failure, or HIV co-infection, MDR-TB treatment should be considered regardless of the trimester. MDR-TB regimen should be individualized and started in sufficient time to achieve smear conversion before delivery. • If an injectable has to be used, capreomycin may be a better option than other injectables—belonging to the FDA drug safety class “C”. If possible, avoid ethionamide because it increases the nausea and vomiting associated with pregnancy.
MDR-TB and children	<ul style="list-style-type: none"> • The low bacillary load and the difficulty in obtaining specimens make it difficult to confirm the diagnosis microbiologically. The DST pattern of the index case should be used if no isolates are available from the child. • The criteria for designing an MDR-TB regimen are the same as in the adults, with the difference that probably three effective drugs may be sufficient, given the paucibacillary nature of the disease. One or two drugs from group 4 should be included in the regimen together with one SL I and one FQ. • SLDs seem to be well tolerated by children and treatment outcomes are positive, which is also the case in HIV high-prevalence settings.
MDR-extra-pulmonary TB	<ul style="list-style-type: none"> • Extra-pulmonary MDR-TB is not very frequent. • The treatment of MDR-TB follows the same approach as in the case of pulmonary disease. However, the different capacity of SLD to penetrate different tissues should be taken into consideration when designing the regimen. • RIF, INH, PZA, Eth/Pth, Cs and FQs have good penetration into the CSF, while injectables penetrate only in the presence of inflammation, and PAS and ETB have poor penetration.
Special care in M/XDR-TB	<ul style="list-style-type: none"> • Given the long duration of M/XDR-TB treatment, the common drug-related side effects, and the frequently debilitated condition in the presence of advanced disease or co-infection with HIV, additional intervention are needed to support patients. • Palliative care and ancillary drugs for the management of adverse reactions, nutritional support, but also psychological, social and sometimes financial support. • These interventions can improve the adherence of the patients to treatment, alleviate their suffering and help to achieve favorable outcomes, and they should be considered as “an additional drug” in the treatment of M/XDR-TB.
Model of care for M/XDR-TB	<ul style="list-style-type: none"> • Ambulatory care rather than models of care based mainly on hospitalization are recommended for MDR-TB patient management, and in countries with a massive increase in the number of M-XDR/TB cases detected, decentralization becomes the only solution. • There are positive experiences and good outcomes with community-based models for MDR-TB management, and evidence that a decentralized model may reduce costs. • Ideally, the model of care should be tailored on the specific needs of each patient, but obviously this could not be feasible for large-scale implementation of PMDT (programmatic management of drug-resistant TB), and most countries need to define a model that better fits their reality and available resources.

positive experiences from Bangladesh [30], Cameroon, and other countries should provide the impetus for massive investment in the research of shorter and better-tolerated regimens. In fact, it is only with shorter and less toxic regimens that patient adherence and favorable outcomes will be achieved and that the TB transmission chain will be broken. Finally, controlling DR-TB will be possible only when the ongoing transmission of the disease is limited through the implementation of effective infection control measures and through the concrete expansion of antiretroviral treatment for HIV patients before their immune status declines. Once again, a strong commitment is needed at all levels, as many battlefronts remain in the fight against *M. tuberculosis*.

Compliance with Ethics Guidelines

Conflict of Interest Anna Scardigli and José A. Caminero declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

References

- World Health Organization. Global tuberculosis report 2012. World Health Organization Document 2012;WHO/HTM/TB/2012.6:1-272.
- Shah NS, Richardson J, Moodley P, Moodley S, Babaria P, Ramtahal M, et al. Increasing drug resistance in extensively drug-resistant tuberculosis, South Africa. *Emerg Infect Dis*. 2011;17:510–3.
- Klopper M, Warren RM, Hayes C, Gey van Pittius NC, Streicher EM, Müller B, et al. Emergence and spread of extensively and totally drug-resistant tuberculosis, South Africa. *Emerg Infect Dis*. 2013;19:449–55.
- Velayati AA, Masjedi MR, Farnia P, Tabarsi P, Ghanavi J, Zia Zarifi AH, et al. Emergence of new forms of totally drug-resistant tuberculosis bacilli. Super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. *Chest*. 2009;136:420–5.
- Migliori GB, Lange C, Centi R, Sotgiu G, Mütterlein R, Hoffmann H, et al. Resistance to second-line injectables and treatment outcomes in multidrug-resistant and extensively drug-resistant tuberculosis cases. *Eur Respir J*. 2008;31:1155–9.
- Laniado-Laborín R, Palmero DJ, Caminero-Luna JA. Diagnosis and treatment of multidrug-resistant tuberculosis in developed and developing countries: finally towards equality? *Curr Respir Med Rev*. 2012;8:864–74.
- Caminero JA, Van Deun A, Fujiwara PI, Monedero I, Chiang CY, Rieder HL, et al. Guidelines for clinical and operational management of drug-resistant tuberculosis. Paris: International Union Against Tuberculosis and Lung Disease; 2013. *Very comprehensive and updated guide on the clinical and operational management of MDR-TB. This source has been used for data on diagnosis of DR-TB, M/XDR-TB regimen building and special situations.*
- Caminero JA. Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding. [State of the Art series. Drug-resistant tuberculosis. Number 4 in the series]. *Int J Tuberc Lung Dis*. 2010;14:382–90.
- Monedero I, Caminero JA. Management of multidrug-resistant tuberculosis: an update. *Ther Adv Respir Dis*. 2010;4:117–27.
- Daley CL, Caminero JA. Management of multidrug resistant tuberculosis. *Semin Respir Crit Care Med*. 2013;34:44–59. *In depth review of the management of M/XDR-TB, with detailed description of first and second line anti-TB drugs and their management.*
- Caminero JA. Management of multidrug-resistant tuberculosis and patients in retreatment. *Eur Respir J*. 2005;25:928–36.
- World Health Organization. Definitions and reporting framework for tuberculosis - 2013 revision. World Health Organization Document 2013;WHO/HTM/TB/2013.2:1-40.
- Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. 2010;363:1005–15.
- Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet*. 2011;377:1495–505. *Interesting study from 6 countries in 3 continents, to evaluate the decentralized use of Xpert MTB/RIF.*
- World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. World Health Organization Document 2011;WHO/HTM/TB/2011.4:1-27.
- Nicol MP, Zar HJ. New specimens and laboratory diagnostics for childhood pulmonary TB: progress and prospects. *Paediatr Respir Rev*. 2011;12:16–21.
- Whittaker E, Jones C, Kampmann B. Chapter 15. TB in children. *Eur Respir Monogr*. 2012;58:206–18.
- Tortoli E, Russo C, Persimoni C, Mazzola E, Dal Monte P, Pascarella M, et al. Clinical validation of Xpert MTB/RIF for the diagnosis of extrapulmonary tuberculosis. *Eur Respir J*. 2012;40:442–7.
- Weyer K, Mirzayev F, Migliori GB, van Gemert W, D'Ambrosio L, Zignol M, et al. Rapid molecular TB diagnosis: evidence, policy making and global implementation of Xpert MTB/RIF. *Eur Respir J*. 2013;42:252–71. *Detailed analysis of the existing evidence with Xpert MTB/RIF technology and on how and when use it. This article emphasizes also the important increase in the number of MDR-TB cases detected through this technology.*
- Hillemann D, Rüsche-Gerdes S, Richter E. Feasibility of the GenoType MTBDRsl assay for fluoroquinolone, amikacin-capreomycin, and ethambutol resistance testing of *Mycobacterium tuberculosis* strains and clinical specimens. *J Clin Microbiol*. 2009;47:1767–72.
- Barnard M, Warren R, Gey van Pittius N, van Helden P, Bosman M, Streicher E, et al. GenoType MTBDRsl line probe assay shortens time to diagnosis of extensively drug-resistant tuberculosis in a high-throughput diagnostic laboratory. *Am J Respir Crit Care Med*. 2012;186:1298–305.
- Caminero JA, Matteelli A, Lange C. Chapter 12. Treatment of TB. *Eur Respir Monogr*. 2012;58:154–66.
- Caminero JA. Treatment of multidrug-resistant tuberculosis: evidence and controversies. *Int J Tuberc Lung Dis*. 2006;10:829–37. *Analysis of the most controversial issues in the management of MDR-TB such the confirmation of MDR-TB diagnosis, the selection of drugs for its treatment, the duration of intensive phase, the contribution of surgery and the role of standardised and individualized treatment. These issues have been addressed also in the paper, in the light of the current evidence.*
- Falzon D, Jaramillo E, Schünemann HJ, Arentz M, Bauer M, Bayona J, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur Respir J*. 2011;38:516–28.
- World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. 2011 update. World Health Organization Document 2011;WHO/HTM/TB/2011.6:1-33.
- Caminero JA, Sotgiu G, Zumla A, Migliori GB. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis.

- Lancet Infect Dis. 2010;10:621–9. *In depth analysis of the role of the different anti-TB drugs in the treatment of MDR and XDR-TB.*
27. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. World Health Organization Document 2006;WHO/HTM/TB/2006.361:1-174.
 28. • World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. World Health Organization Document 2008;WHO/HTM/TB/2008.402:1-247. *Comprehensive guidelines on DR-TB, with attention also to XDR-TB and HIV.*
 29. Katiyar SK, Bihari S, Prakash S, Mamtani M, Kulkarni H. A randomised controlled trial of high-dose isoniazid adjuvant therapy for multidrug-resistant tuberculosis. In reply. (Correspondence). *Int J Tuberc Lung Dis.* 2008;12:1102.
 30. • Van Deun A, Kya Jai Maug A, Halim MA, Kumar Das P, Ranjan Sarker M, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med.* 2010;182:684–92. *Very relevant observational study to evaluate the effectiveness of standardized regimens for MDR-TB patients, who did not receive SLDs previously, in low income countries. The positive results of the study encourage further evaluation of such shorter regimens.*
 31. Vadwai V, Ajbani K, Jose M, Vineeth VP, Nikam C, Deshmukh M, et al. Can *inhA* mutation predict ethionamide resistance? *Int J Tuberc Lung Dis.* 2013;17:129–30.
 32. Cheng AFB, Yew WW, Chan EWC, Chin ML, Hui MMM, Chan RCY. Multiplex PCR amplicon conformation analysis for rapid detection of *gyrA* mutations in fluoroquinolone-resistant *Mycobacterium tuberculosis* clinical isolates. *Antimicrob Agents Chemother.* 2004;48:596–601.
 33. Johnson JL, Hadad DJ, Boom WH, Daley CL, Peloquin CA, Eisenach KD, et al. Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis.* 2006;10:605–12.
 34. Rustumjee R, Lienhardt C, Kanyok T, Davies GR, Levin J, Mthiyane T, et al. A phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis.* 2008;12:128–38.
 35. Pranger AD, Alffenaar JWC, Aarnoutse RE. Fluoroquinolones, the cornerstone of treatment of drug-resistant tuberculosis: a pharmacokinetic and pharmacodynamic approach. *Curr Pharm Design.* 2011;17:2908–30.
 36. • Johnston JC, Shahidi NC, Sadatsafavi M, FitzGerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. *PLoS ONE.* 2009;4(9):e6914. doi:10.1371/journal.pone.0006914. *Interesting review of the outcomes of MDR-TB patients from 31 programmes and 21 countries, evaluating the factors associated to successful outcomes and those associated to worse outcomes (ex. resistance to FQs). The important role of FQs is therefore evident.*
 37. • Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB. Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. *Clin Infect Dis.* 2010;51:6–14. *Review of the outcomes of XDR-TB patients from 13 observational studies, evaluating also the impact of the FQ use in the outcomes. The important role of FQs is also here evident.*
 38. • Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox HS, Holtz TH, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. *Eur Respir J.* 2013;42:156–68. *Interesting comparison of the successful outcomes in MDR-TB patients with or without additional resistance to FQs and/or SLDs. The important role of FQs is also here evident.*
 39. • Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis.* 2012;16:447–54.
 40. • Sotgiu G, Centis R, D'Ambrosio L, Alffenaar JWC, Anger HA, Caminero JA, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J.* 2012;40:1430–42. *Analysis of 12 studies to assess the efficacy and tolerability of Linezolid - including when given at lower (<600mg/day) and higher (>600mg/day) dosages.*
 41. Singla R, Caminero JA, Jaiswal A, Singla N, Gupta S, Bali RK, et al. Linezolid: an effective, safe and cheap drug for patients failing multidrug-resistant tuberculosis treatment in India. *Eur Respir J.* 2012;39:956–62.
 42. Ntziora F, Falagas ME. Linezolid for the treatment of patients with mycobacterial infections: a systematic review. [Erratum appears in *Int J Tuberc Lung Dis* 2007;11:936]. *Int J Tuberc Lung Dis.* 2007;11:606–11.
 43. Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med.* 2012;367:1508–18.
 44. Koh WJ, Kwon OJ, Gwak H, Chung JW, Cho SN, Kim WS, et al. Daily 300 mg dose of linezolid for the treatment of intractable multidrug-resistant and extensively drug-resistant tuberculosis. *J Antimicrob Chemother.* 2009;64:388–91.
 45. Chang KC, Yew WW, Cheung SW, Leung CC, Tam CM, Chau CH, et al. Can intermittent dosing optimize prolonged linezolid treatment of difficult multidrug-resistant tuberculosis? *Antimicrob Agents Chemother.* 2013;57:3445–9.
 46. • Gopal M, Padayatchi N, Metcalfe JZ, O'Donnell MR. Systematic review of clofazimine for the treatment of drug resistant tuberculosis. *Int J Tuberc Lung Dis.* 2013;17:1001–7. *Recent interesting evaluation of 9 studies to assess the outcomes of MDR-TB and XDR-TB patients receiving Clofazimine.*
 47. Payen MC, De Wit S, Martin C, Sergysels R, Muylle I, Van Laethem Y, et al. Clinical use of the meropenem-clavulanate combination for extensively drug-resistant tuberculosis. *Int J Tuberc Lung Dis.* 2012;16:558–60.
 48. England K, Boshoff HIM, Arora K, Weiner D, Dayao E, Schimel D, et al. Meropenem-clavulanic acid shows activity against *Mycobacterium tuberculosis in vivo*. *Antimicrob Agents Chemother.* 2012;56:3384–7.
 49. Solapure S, Dinesh N, Shandil R, Ramachandran V, Sharma S, Bhattacharjee D, et al. *In vitro* and *in vivo* efficacy of β -lactams against replicating and slowly growing/nonreplicating *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother.* 2013;57:2506–10.
 50. De Lorenzo S, Alffenaar JW, Sotgiu G, Centis R, D'Ambrosio L, Tiberi S, et al. Efficacy and safety of meropenem-clavulanate added to linezolid-containing regimens in the treatment of MDR-/XDR-TB. *Eur Respir J.* 2013;41:1386–92.
 51. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis. Interim policy guidance. World Health Organization Document 2013;WHO/HTM/TB/2013.6:1-57.
 52. Van Deun A, Hamid Salim MA, Kumar Das AP, Bastian I, Portaels F. Results of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh. *Int J Tuberc Lung Dis.* 2004;8:560–7.
 53. Rodriguez M, Monedero I, Caminero JA, Encarnación M, Dominguez Y, Acosta I, et al. Successful management of multidrug-resistant tuberculosis under programme conditions in the Dominican Republic. *Int J Tuberc Lung Dis.* 2013;17:520–5.
 54. Seddon JA, Godfrey-Faussett P, Jacobs K, Ebrahim A, Hesselring AC, Schaaf HS. Hearing loss in patients on treatment for drug-resistant tuberculosis. *Eur Respir J.* 2012;40:1277–86.
 55. Peloquin CA, Beming SE, Nitta AT, Simone PM, Goble M, Huitt GA, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. *Clin Infect Dis.* 2004;38:1538–44.
 56. Brust JCM, Lygizos M, Chaiyachati K, Scott M, van der Merwe TL, Moll AP, et al. Culture conversion among HIV co-infected multidrug-resistant tuberculosis patients in Tugela Ferry, South Africa. *PLoS ONE.* 2011;6(1):e15841. doi:10.1371/journal.pone.0015841.
 57. Gammino VM, Taylor AB, Rich ML, Bayona J, Becerra MC, Bonilla C, et al. Bacteriologic monitoring of multidrug-resistant tuberculosis

- patients in five DOTS-Plus pilot projects. *Int J Tuberc Lung Dis.* 2011;15:1315–22.
58. Chan CY, Au-Yeang C, Yew WW, Hui M, Cheng AFB. Postantibiotic effects of antituberculosis agents alone and in combination. *Antimicrob Agents Chemother.* 2001;45:3631–4.
59. • Marrone MT, Venkataramanan V, Goodman M, Hill AC, Jereb JA, Mase SR. Surgical interventions for drug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis.* 2013;17:6–16. *Interesting meta-analysis of studies published between 1975 and 2013 to assess the association between surgery and successful treatment of M/XDR-TB compared to non-surgical interventions.*
60. Dravniece G, Cain KP, Holtz TH, Riekstina V, Leimane V, Zaleskis R. Adjunctive resectional lung surgery for extensively drug-resistant tuberculosis. *Eur Respir J.* 2009;34:180–3.
61. Chan ED, Iseman MD. Surgery for MDR-TB? (Correspondence). *Int J Tuberc Lung Dis.* 2013;17:710.